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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,979	01/24/2002	William Melvin	1012-103US	2841

22798 7590 10/17/2007

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
10/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/936,979	MELVIN ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-9* is/are allowed.

6)☒ Claim(s) *10-12 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 7/30/2007 in response to the previous Non-Final Office Action (05/07/2007) is acknowledged and has been entered.

Claims 1-12 and 14-17 are currently pending and under consideration.

Rejections Withdrawn:

The rejection of claim 15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants amendments.

The rejection of claim 18 under 35 U.S.C. 112, first paragraph, enablement is withdrawn in view of Applicants amendments which cancels claim 18.

New Rejections upon Reconsideration:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-12 and 15 are rejected under 35 U.S.C. 102(b) as anticipated by Melvin et al. (WO 97/12246, 1997, IDS, *of record*).

Melvin et al. teach monoclonal and polyclonal antibodies that bind to p450 CYP1B1 protein. Specifically, the WO document teaches that antibodies which react with human p450 CYP1B1 protein can be generated by using a preparation of non-human CYP1B1 protein, e.g., murine CYP1B1 (beginning on page 8, *Preparation of antibodies*). Thus, while Melvin et al. do not explicitly teach that the monoclonal antibodies recognize an epitope in the cytochrome P450 CYP1B1 protein included within the amino acid sequence VNQWSVNHDPVKWPN or PExFDPARFLDKDGy,

wherein X is D or N and y is L or F, the claimed limitation does not appear to result in a manipulative difference between the prior art's antibodies because the specification teaches (page 26, lines 4-17) that amino acid residues FDPARFLDKDG are identical in three p450's, rat CYP1B1, mouse CYP1B1 and human CYP1B1. Thus, the claimed antibody appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Note: In order to expedite prosecution, the Examiner would like to respond to Applicants arguments filed on 1/22/2007 pertaining to the previous citation of Melvin in the Non-Final rejection of 9/12/2006. In response to this rejection, Applicants assert that Melvin did not raise polyclonal or monoclonal to whole CYP1B1 or to the polypeptides cited in claim 10. In particular, Applicants assert that the rejection can only hinge on the teachings at page 9 of Melvin, that methods exist in the universe to raise antibody preparations against CYP1B1. However, Applicants assert that such a rejection can not stand because this does not teach, or inherently teach, an isolated monoclonal antibody that recognizes an epitope that binds to the specific amino acids sequences VNQWSVNHDPVKWPN or PExFDPARFLDKDGy, wherein x is D or N and y is L or F. In addition, Applicants note that the preparation of monoclonal antibodies to whole CYP1B1 does not necessarily provide the isolated antibodies of claim 10, and therefore the claim is not anticipated by Melvin. For example, Applicants assert that monoclonal antibodies are generally isolated by, e.g., exposing a mouse to an antigen of interest, harvesting activated B-lymphocytes from the spleen of the mouse, fusing the lymphocytes with immortal cells to form a hybridoma possibly expressing a single antibody to a single epitope of the antigen, screening the hybridomas for expression of an antibody of interest and cloning a hybridoma expressing an antibody of interest. In addition, Applicants assert that any given monoclonal antibody randomly raised against full length CYP1B1 would be unlikely to be specific to the cited amino acid sequences; and screening techniques to specifically select the cited sequences are not taught in the art. In particular, Applicants assert that efforts to raise monoclonal antibodies to an antigen do not result in isolation of antibodies to

epitopes including all sequences of an antibody. As such, Applicants assert that monoclonal antibodies prepared against CYP1B1 would not inherently recognize any particular epitope of CYP1B1, an certainly not inherently recognize epitopes of the sequences cited in claim 10.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner acknowledges and concedes that Melvin et al. does not explicitly teach raising antibodies to the specific peptides consisting of the amino acid sequences recited in claim 10. However, the Examiner recognizes that the claims do not appear to be limited to only antibodies which are raised to those specific sequences. In contrast, the Examiner recognizes that the instant claims recite an isolated monoclonal antibody which is capable of specifically binding to cytochrome p450 CYP1B1, wherein the monoclonal antibody recognizes an epitope in the cytochrome p450 CYP1B1 protein included within the amino acid sequence of VNQWSVNHDPVKWPN or PExFDPARFLDKDGy, wherein x is D or N and y is L or F (emphasis added). Thus, the monoclonal antibodies which specifically bind to CYP1B1 taught by Melvin et al. appear to meet the claimed functional limitation of binding to CYP1B1. With regards to recognizing a particular epitope, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Thus, while the Examiner has considered Applicants remarks on how difficult it is to generate a monoclonal antibody which recognizes a particular epitope, Applicants have not provided a patentable difference between the claimed antibody and that disclosed by the prior art. Moreover, as taught in claim 15 of the instant application, the claimed monoclonal antibody of claim 10 is obtained by immunizing an animal with a peptide comprising the amino acid sequence of VNQWSVNHDPVKWPN or PExFDPARFLDKDGy, wherein x is D or N and y is L or F, which is conjugated to an immunogenic carrier (emphasis added); sacrificing the animal and fusing the spleen cells obtained from the animal with myeloma cells to produce one or more hybridomas; and (c) screening the hybridomas for antibodies capable of binding the peptide. Thus, it appears that the antibodies are obtained via detecting the binding of the antibody to the peptide and not the individual epitopes.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-12 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pottenger et al. (Arch. Biochem. Biophys. 1991; 286: 488-497, of record) as evidenced by Accession Number NP_034124 (of record) in view of Cambell, A.M. (Monoclonal Antibody Technology, Elsevier Science, NY, 1986, pages 1-33).

Pottenger et al. teach polyclonal antibodies raised to a protein referred to as P450-EF isolated from mouse embryo fibroblast derived C3H/10T1/2 CL8 cells (abstract and page 490, 1st column, *Immunological Studies*). Thus, while Pottenger et al. do not specifically teach that the protein referred to as P450-EF is synonymous with P450 CYP1B1, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art because Accession Number NP_034124 (see below) refers to P450-EF in the Pottenger et al. reference as P450 CYP1B1.

Pottenger et al. do not explicitly teach monoclonal antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the protein referred to as P450-EF as taught by Pottenger et al. for the purposes of generating antibodies that specifically bind to the claimed peptides. One would have been motivated to do so because it is conventional in the art to generate antibodies following the cloning of a gene. Campbell, A..M. teaches (page 29) that it is "customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)". Further, the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious. See Ex parte Ehrlich, 3 USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. APp. & Int. 1990).

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REFERENCE   26 (residues 1 to 543)
  AUTHORS   Pottenger,L.H., Christou,M. and Jefcoate,C.R.
  TITLE     Purification and immunological characterization of a novel
            cytochrome P450 from C3H/10T1/2 cells
  JOURNAL   Arch. Biochem. Biophys. 286 (2), 488-497 (1991)
   PUBMED   1910294
COMMENT     PROVISIONAL REFSEQ: This record has not yet been subject to final
            NCBI review. The reference sequence was derived from U03283.1.
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      121 asfrvvsggr slafghyseh wktqrrsays tmrafstrhp rsrgllegha laearelvav
      181 lvrrcaggaf ldptqpviva vanvmsavcf gcrynhddae flellshnee fgrtvgagsl
      241 vdvlpwlqlf pnpvrttfrk feqlnrnfsn fvldkflrhr eslvpgaapr dmtdafilsa
      301 ekkasgapgd dssgldledv patitdifga sqdtlstall wllilftryp dvqarvqael
      361 dqvvgrdrlp cmsdqpnlpy vmaflyesmr fssflpvtip hattantfvl gyyipkntvv
      421 fvnqwsvnhd pakwpnpedf dparfldkdg finkalassv mifsvgkrrc igeelskmll
      481 flfisilahq cnfkanqnes snmsfsyglt ikpksfrihv slresmelld navkklqtee
      541 gck
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Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melvin et al. (WO 97/12246, 1997, IDS, *of record*) in view of Chiocca et al. (US 5,688,773, 1997, *of record*).

Melvin et al. teach, as applied to claims 10-12 and 15 above, monoclonal and polyclonal antibodies that bind to p450 CYP1B1 protein. Specifically, the WO document teaches that antibodies that react with human p450 CYP1B1 protein can be generated by using a preparation of non-human CYP1B1 protein, e.g., murine CYP1B1 (beginning on page 8, *Preparation of antibodies*). Moreover, the Wo document teaches that the antibodies are used in tumor diagnosis by detecting CYP1B1 (page 7, 2nd full paragraph).

Melvin et al. do not explicitly teach that the antibody is labeled.

Chiocca et al. teach that the expression of nonhuman or unique surface antigens in neoplastic cells can be located on such neoplastic cells by subsequence biding with labeled antibodies (column 13, lines 24-26).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to label an antibody as taught by Melvin et al. in view of Chiocca et al. One would have been motivated to do so because Chiocca et al. teach labeled antibodies are used to identity the expression patterns of unique surface antigens present on neoplastic cells. As such, labeling antibodies for purposes of determining expression patterns of a surface antigen on neoplastic cells is well known in the art. Thus, one of ordinary skill in the art would have a reasonable expectation that by labeling an antibody taught by Melvin et al., one would achieve a method of measuring the expression patterns of CYP1B1 on neoplastic cells for the purposes of diagnosis.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Melvin et al. (WO 97/12246, 1997, IDS, *of record*) in view of Queen et al. (WO 90/07861, 1990), Kettleborough et al. (Protein Engineering 1991; 4: 773-783) and Devaux et al (U.S. Patent 6,824,780 B1, 10/29/1999).

Melvin et al. teach, as applied to claims 10-12 and 15 above, monoclonal and polyclonal antibodies that bind to p450 CYP1B1 protein. Specifically, the WO document teaches that antibodies that react with human p450 CYP1B1 protein can be generated by using a preparation of non-human CYP1B1 protein, e.g., murine CYP1B1 (beginning on page 8, *Preparation of antibodies*).

Moreover, the Wo document teaches that the antibodies are used in tumor diagnosis by detecting CYP1B1 (page 7, 2nd full paragraph).

Melvin et al. do not explicitly teach that the antibody is a humanized antibody.

Kettleborough et al. teach the humanization mouse monoclonal antibodies since mouse monoclonal antibodies elicit an immune response in human patients (page 773, 1st column, 1st paragraph).

Queen et al. teach methods for designing humanized immunoglobulins (abstract).

Devaux et al also discloses the generation of humanized antibodies. Specifically, Devaux et al. teach that humanized antibodies are better suited for human therapy because they reduce immunogenicity and human anti-mouse antibody (HAMA) response (see columns 23-24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to humanize the antibody taught by Melvin et al. in view of the teachings of Queen et al., Kettleborough et al. and Devaux et al.. One would have been motivated to do so because the humanization of antibodies is well known; and further reduce immunogenicity and HAMA response. Thus, one of ordinary skill in the art would have a reasonable expectation that by humanizing the antibody taught by Melvin et al. in view of the teachings of Queen et al., Kettleborough et al. and Devaux et al., one would achieve a antibody with reduced immunogenicity.

Conclusion

In the instant case, Melvin et al. (WO 97/12246, 1997, IDS, of record), considered to be the closest prior art, teaches monoclonal and polyclonal antibodies that bind to p450 CYP1B1 protein, as well as a method of preparing said antibodies. However, Melvin et al. does not teach or suggest a monoclonal antibody or a method of making an antibody that specifically binds to a peptide consisting of an amino acid sequence VNQWSVNHDPVKWPN or PExFDPARFLDKDGy, wherein X is D or N and y is L or F as recited in the pending claims. As such, claims 1-9 appear to be free of the prior art and are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF